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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/813,467	PECK ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-59 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-59 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 6 March 2007 claims 28, 33-34, 36, 54, and 56 were amended, claim 60 was canceled, and new claim 61 was added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

The previous rejections under the judicially created doctrine of obviousness-type double patenting are **maintained**. Applicant states on page 12 of the Remarks filed 6 March 2007 that a Terminal Disclaimer has been filed. However, No Terminal Disclaimer has been received, nor have any fees for the filing of a Terminal Disclaimer been paid.

Claims 28-59 and 61 are under prosecution.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 28-36, 38-44, 46-48, 50-52, 54-59, and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993).

Regarding claim 28, Anderson et al teach a method for producing an addressable array of oligonucleotides on a substrate. In a single exemplary embodiment, Anderson et al teach a membrane incorporating interactive particles (column 6, lines 49-56), wherein the interactive particles are the different locations of the surface of the membrane, which is the substrate. The interactive particles are porous beads (column 21, line 66-column 22, line 3). The porous beads each have different moieties, in the form of different individual molecules, attached thereon. Because the beads are incorporated on the membrane, the locations of the beads are predetermined. The individual molecules detect targets or classes of targets. The porous beads on the membrane are therefore an addressable array in accordance with the definition of an addressable array on page 10, lines 13-26 of the specification. Anderson et al also teach a first nucleotide capped with a trityl group attached to the surface of the support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Regarding claim 29, Anderson et al teach the method of claim 28, wherein a blocked nucleoside monomer is attached to the substrate by contacting the substrate with a fluid comprising a blocked nucleoside monomer at a location on the substrate that comprises hydroxy groups; namely, the blocked monomer in step ii of Table I is added to the unblocked attached nucleotide of step i, which has a free hydroxyl group at the 5′ end generated by the detritylation step (column 19, line 40-column 20, line 50).

Regarding claim 30, Anderson et al teach the method of claim 28, wherein the steps are repeated a plurality of times (column 20, lines 2).

Regarding claim 31, Anderson et al teach the method of claim 28, wherein the substrate comprises a surface of a planar support; namely, the support is a flat disc (column 6, lines 49-56).

Regarding claim 32, Anderson et al teach the method of claim 28, wherein the displacing step causes minimal mixing of deblocking and purging fluids; namely, density differences are used to minimize mixing (column 10, lines 23-24).

Regarding claim 33, Anderson et al teach the method of claim 28, wherein the substrate comprises a surface of a support containable within a flow cell; namely, internal space for fluid flow so as to contact solid support (Column 5, lines 20-38).

Regarding claim 34, Anderson et al teach the method of claim 28, wherein the substrate comprises a nascent surface of a planar support; namely, the support is a flat disc (column 6, lines 49-56), and the reactions are occurring on the nascent surface created by the previous round of reactions (column 20, lines 2).

Regarding claim 35, Anderson et al teach the method of claim 28, wherein the purging fluid has a density that is different from the deblocking fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D).

Regarding claims 36 and 38, Anderson et al teach the method of claim 28, wherein the deblocking fluid and the purging fluid have a density difference, expressed as the Atwood number, of at least about 0.01. In a single exemplary embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10). Detritylation is followed with a wash using acetonitrile as a purging solution, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number.

Regarding claim 39, Anderson et al teach the method of claim 28, wherein the purging fluid is an organic fluid; namely, 50% dichloromethane and 50% dimethylformamide (Table II).

Regarding claim 40, Anderson et al teach the method of claim 28, wherein the purging fluid comprises an oxidizing agent; namely, the purging fluid is interpreted to be all of the fluids of Table I following the deprotection step i (column 20), which are introduced in one long series of changing densities (column 7, lines 5-19). The series that makes up the purging fluid includes the oxidizing agent iodine (step iv of Table I).

Regarding claims 41 and 42, Anderson et al teach the method of claim 28, wherein the purging fluid comprises a wash fluid; namely, step 3 of Table II is a washing step using 50% dichloromethane and 50% dimethylformamide (Table II).

Regarding claim 43, Anderson et al teach the method of claim 41, wherein the wash fluid is acetonitrile (column 13, line 67-column 14, line 1).

Regarding claim 44, Anderson et al teach the method of claim 28, wherein the deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D).

Regarding claim 46, Anderson et al teach the method of claim 28, wherein the purging fluid limits the efficiency of the deblocking fluid; namely, the deblocking reaction requires acid (e.g., dichloroacetic acid; step i of Table I). Addition of any washing fluid decreases the concentration of acid, thereby limiting the efficiency of deblocking.

Regarding claim 47, Anderson et al teach the method of claim 29, wherein the hydroxyl groups are 5' OH groups of nucleoside polymers deblocked by the detritylation step (column 19, line 40-column 20, line 50).

Regarding claim 48, Anderson et al teach the method of claim 28, wherein the step of displacing occurs within a flow cell; namely, an internal space for fluid flow so as to contact a solid support (column 5, lines 20-38).

Regarding claim 50, Anderson et al teach the method of claim 28, wherein the blocking group is a trityl group (column 19, line 40-column 20, line 50), which is an acid sensitive group, and the deblocking fluid comprises dichloroacetic acid (step i of Table I).

Regarding claim 51, Anderson et al teach the method of claim 33, wherein the substrate is contained within a chamber of flow cell; namely, chamber 24 is which holds the particulate material (i.e., the substrate; figure 1 and column 11, line 24-column 12, lines 27). Chamber 24 is also connected to upper and lower fluid lines 100 and 102 (Figure 1), which are interpreted as fluid inlet and outlets.

Regarding claim 52, Anderson et al teach the method of claim 51, wherein the flow cell is oriented an at least partially vertical position; namely, the flow cell is attached to a rotor system, and is spun with the axis vertically (Abstract).

Regarding claim 54, Anderson et al teach the method of claim 28, wherein the deblocking fluid comprises an organic solvent; namely, acetonitrile (column 13, line 67-column 14, line 1). The vapor pressure of acetonitrile at 0°C and 1 ATM pressure is 24.75 mm Hg, which is 3.3 kPa.

Regarding claim 55, Anderson et al teach the method of claim 28, further comprising contacting the substrate comprising the attached blocked nucleoside polymer with an oxidation fluid prior to contacting with the deblocking fluid; namely, oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv).

Regarding claim 56, Anderson et al teach a method for producing an addressable array comprising a substrate and at least two oligonucleotides bonded to different locations on a surface of said substrate. In a single exemplary embodiment, Anderson et al teach a membrane incorporating interactive interactive particles (column 6, lines 49-56), wherein the interactive particles are the different locations of the surface of the membrane, which is the substrate. The interactive particles are porous beads (column

21, line 66-column 22, line 3). The porous beads each have different moieties, in the form of different individual molecules, attached thereon. Because the beads are incorporated on the membrane, the locations of the beads are predetermined. The individual molecules detect targets or classes of targets. The porous beads on the membrane are therefore an addressable array in accordance with the definition of an addressable array on page 10, lines 13-26 of the specification.

Anderson et al teach contacting tritylated nucleoside monomers with the supports, wherein terminal nucleotides on the supports have been previously detritylated to provide free 5'OH groups (column 19, line 40-column 20, line 50), wherein the 5' OH groups are the functional groups on the surface that bind the blocked (i.e., tritylated) monomers to the locations on the surface. Anderson et al also teach the newly attached nucleosides are subsequently detritylated (column 19, line 40-column 20, line 50), wherein the detritylation fluid is a deblocking fluid (Table I, step i, column 20). Anderson et al further teach washing the surface (Table I, column 20), wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). The washing solution is a purging solution that displaces the deblocking fluid from all of the locations. Anderson et al also teach reacting the newly unblocked monomers at the locations with another blocked nucleoside monomer; namely, the steps of the method are repeated on the substrate to attain the required chain length (column 20, line 2).

Regarding claim 57, Anderson et al teach the method of claim 56, wherein the at least two oligonucleotides comprise the same sequence; namely, the solutions are added to the support in a rotor (column 20, lines 55-65), which is interpreted as a single synthesis in a single rotor, producing one full length sequence at more than one location on the support.

Regarding claim 58, Anderson et al teach the method of claim 56, wherein the at least two oligonucleotides comprise different sequences; namely, at least one location has a failure sequence

(column 20, lines 10-25), which is interpreted as a second different sequence in addition to the successfully synthesized sequences.

Regarding claim 59, Anderson et al teach the method of claim 56, further comprising contacting the substrate comprising the bonded blocked nucleoside polymer with an oxidation fluid prior to contacting with the deblocking fluid; namely, oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv).

Regarding claim 61, Anderson et al teach the method of claim 28, wherein the substrate is planar; namely, the membrane is a flat disk (column 6, lines 49-56).

Response to Arguments

Applicant's arguments filed 6 March 2007 (i.e., the "Remarks") have been fully considered but they are not persuasive for the reason(s) listed below.

A. Applicant argues on pages 8-9 of the Remarks that Anderson et al does not teach an addressable array. Applicant relies upon the definition on page 10, lines 15-19 of the specification, wherein an addressable array required multiple regions of different moieties such that a region at a particular predetermined location on the array will detect a particular target or class of targets.

However, as noted above, Anderson et al do teach an addressable array; namely, Anderson et al teach a membrane incorporating interactive particles (column 6, lines 49-56), wherein the interactive particles are the different locations of the surface of the membrane, which is the substrate. The interactive particles are porous beads (column 21, line 66-column 22, line 3). The locations are predetermined because the interactive particles are incorporated into the membrane before synthesis on the interactive particles takes place (column 6, lines 9-56). Thus, Anderson et al teach a substrate in the form of a membrane, having multiple regions in the form of the multiple interactive particles (i.e., beads) incorporated into the membrane. The "different moieties" of the array are the oligonucleotides that are synthesized on the regions (i.e., interactive particles) within the membrane. The oligonucleotides will

detect a target or a class of targets in the form of nucleic acids in a sample that will bind to the oligonucleotides of Anderson et al. Thus, Anderson et al teach an addressable array in accordance with the definition on page 10, lines 15-19 of the specification.

B. Applicant further argues on pages 8-9 of the Remarks that because the solid support is uniformly contacted with the same reagents in a centrifugal synthesizer, Anderson does not teach the production of an array that contains different chemical moieties at the particular predetermined locations.

However, it is noted that page 10, lines 15 to 19 of the specification requires "multiple regions of different moieties (e.g., different polynucleotide sequences)...." Thus, the different moieties are not limited to different polynucleotide sequences, but encompasses "different moieties" in the form of different molecules having the same sequence attached at multiple different regions of the array.

Thus, even though the array substrate is uniformly contacted with the same reagents, each predetermined location (i.e., interactive particle) of the array has a different moiety, in the form of different individual molecules having the same sequence, attached thereon. Thus, the claim has been given the broadest reasonable interpretation consistent with the specification (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1]).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 28 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Greene et al (*Protective Groups in Organic Synthesis*, 3rd ed., Wiley and Sons, New York, 1999, page 106).

Regarding claim 37, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a membrane incorporating interactive particles (column 6, lines 49-56), wherein the interactive particles are the different locations of the surface of the membrane, which is the substrate. The interactive particles are porous beads (column 21, line 66-column 22, line 3). The porous beads each have different moieties, in the form of different individual molecules, attached thereon. Because the beads are incorporated on the membrane, the locations of the beads are predetermined. The individual molecules detect targets or classes of targets. The porous beads on the membrane are therefore an addressable array in accordance with the definition of an addressable array on page 10, lines 13-26 of the specification. Anderson et al also teach a first nucleotide capped with a trityl group attached to the surface of the support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al

also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method wherein the deblocking fluid and the purging fluid have a density difference. Detritylation is followed with a wash using dichloromethane as a purging solution, which has a density of 1.325 g/mL (Table I, step i). Anderson et al also teach that a series of solutions (i.e., the deblocking fluid and purging fluid) is added in either increasing or decreasing density (column 20, lines 55-64).

Anderson et al do not explicitly teach the purging fluid density is higher than the deblocking fluid density.

However, Green et al teach the deblocking (i.e., cleavage) of dimethoxytrityl (i.e., trityl) groups of deoxyribonucleotides using 3% trichloroacetic acid (density 1.62 g/mL) in 95:5 nitromethane/methanol (densities 1.127 and 0.791 g/mL, respectively), with the added advantage that the mixture reduces the levels of depurination of the reaction product (page 106). Depurination results in a degraded product on the array.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not posses characteristic relied on" (205 USPQ 594, second column, first full paragraph). In the instant case, the solvent mixture is predominantly nitromethane, with a density of 1.127 g/mL, with 5% methanol, having a lower density. A final concentration of 3% of the higher density trichloroacetic acid is believed to produce a solution with an overall density nearly equal to that of nitro methane, because similar percentages of both a higher density liquid and a lower density liquid are added. Thus, the final density of the solution of Greene et al is believed to be lower that 1.325 g/mL, which is the density of the purging fluid of Anderson et al.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Anderson et al with a deblocking solution of lower density as taught by Greene et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having fewer degraded products on the array via a reduction in the levels of depurination of the reaction product as explicitly taught by Greene et al (page 106).

9. Claims 28 and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Mian et al (U.S. Patent No. 6,319,469, issued 20 November 2001).

Regarding claim 45, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a membrane incorporating interactive particles (column 6, lines 49-56), wherein the interactive particles are the different locations of the surface of the membrane, which is the substrate. The interactive particles are porous beads (column 21, line 66-column 22, line 3). The porous beads each have different moieties, in the form of different individual molecules, attached thereon. Because the beads are incorporated on the membrane, the locations of the beads are predetermined. The individual molecules detect targets or classes of targets. The porous beads on the membrane are therefore an addressable array in accordance with the definition of an addressable array on page 10, lines 13-26 of the specification. Anderson et al also teach a first nucleotide capped with a trityl group attached to the surface of the support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density

(column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method of claim 44, wherein the deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D).

While Anderson et al are silent with respect to specific flow rates, Anderson et al do teach the method wherein the flow rate is controlled and monitored during passage of reagents (column 5,lines 25-27 and column 14, lines 44-53 21). Anderson et al further teach that it is advantageous to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (column 21, lines 30-65). Thus, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step.

In addition, Mian et al teach a method of synthesizing oligonucleotides on a disc (Figure 23b and column 5, lines 65-67), wherein the flow rates are from about 1 cm/sec to about 20 cm/sec having the added advantage that variable flow rates within the claimed range allow fluid transfer over a wide range of times scales as required by the various processes (column 12, lines 40-57).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the flow rates of the method of Anderson et al to with range of flow rates as taught by Mian et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having flow rates that allow fluid transfer over a wide range of times scales as required by the various processes as explicitly taught by Mian et al (column 12, lines 40-57).

10. Claims 28-29 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Gamble et al (U.S. Patent No. 5,874,554, issued 23 February 1999).

Regarding claim 49, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a membrane incorporating interactive particles (column 6, lines 49-56), wherein the interactive particles are the different locations of the surface of the membrane, which is the substrate. The interactive particles are porous beads (column 21, line 66-column 22, line 3). The porous beads each have different moieties, in the form of different individual molecules, attached thereon. Because the beads are incorporated on the membrane, the locations of the beads are predetermined. The individual molecules detect targets or classes of targets. The porous beads on the membrane are therefore an addressable array in accordance with the definition of an addressable array on page 10, lines 13-26 of the specification. Anderson et al also teach a first nucleotide capped with a trityl group attached to the surface of the support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method of claim 29, wherein a blocked nucleoside monomer is attached to the substrate by contacting the substrate with a fluid comprising a blocked nucleoside monomer at a location on the substrate that comprises hydroxy groups; namely, the blocked monomer in

step ii of Table I is added to the unblocked attached nucleotide of step i, which has a free hydroxyl group at the 5' end generated by the detritylation step (column 19, line 40-column 20, line 50).

Anderson et al does not teach deposition by pulse-jetting.

However, Gamble et al teach a method of synthesizing oligonucleotides by pulse jetting monomers (Abstract, line 1) with the added benefit that pulse jetting reduces reagent waste (column 1, lines 50-55).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Anderson et al with the pulse jetting of monomers as taught by Gamble et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted a method of producing an addressable array having the added advantage of reduced reagent waste as explicitly taught by Gamble et al (column 1, lines 50-55).

11. Claims 28, 44 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (U.S. Patent No. 5,186,824, issued 16 February 1993) in view of Farr (U.S. Patent No. 3,969,250, issued 13 July 1976).

Regarding claim 53, Anderson et al teach the method of claim 28 for synthesizing an oligonucleotide on a substrate. In a single exemplary embodiment, Anderson et al teach a membrane incorporating interactive particles (column 6, lines 49-56), wherein the interactive particles are the different locations of the surface of the membrane, which is the substrate. The interactive particles are porous beads (column 21, line 66-column 22, line 3). The porous beads each have different moieties, in the form of different individual molecules, attached thereon. Because the beads are incorporated on the membrane, the locations of the beads are predetermined. The individual molecules detect targets or classes of targets. The porous beads on the membrane are therefore an addressable array in accordance with the definition of an addressable array on page 10, lines 13-26 of the specification. Anderson et al

also teach a first nucleotide capped with a trityl group attached to the surface of the support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D). Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20).

Anderson et al also teach the method of claim 44, wherein the deblocking fluid is displaced with a purging fluid in a manner that moves a stratified interface across the surface; namely, interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D).

Anderson et al does not teach a pressure gradient.

However, Farr teaches stratification of liquids using a pressure gradient; namely, creation of supernatant fluid by centrifuging immiscible liquids (column 1, lines 5-10) with the added advantage that the stratification (i.e., the creation of a supernatant) eliminates the need for decanting, thereby minimizing labor and possible contamination of the sample (column 2, lines 24-26).

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the method comprising a stratified interface as taught by Anderson et al by using a pressure gradient as taught by Farr with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of minimizing labor and possible contamination of the sample as explicitly taught by Farr (column 2, lines 24-26).

Response to Arguments

Applicant's remaining arguments on pages 10-12 of the Remarks rely on arguments set forth to address the rejections of the claims as anticipated by Anderson et al under 35 USC 102(b). These arguments are addressed on pages 8-9 above. Since the arguments regarding the teachings of Anderson et al were not persuasive, the remaining rejections of the claims are maintained.

Conclusion

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

14. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER